REMARKS

Applicant respectfully requests reconsideration. Claims 1, 2, 22 and 34-59 were previously pending in this application. Claims 1 and 36-41 have been amended. Claims 1 and 39-41 were amended to correct minor typographical errors. Claims 36-38 were amended to change the recitation of "functional portion" to "antigen binding portion". As a result, claims 1, 2, 22, 34-38 and 40 are pending for examination with claims 1 and 40 being independent claims. No new matter has been added.

Objections to the Specification

The Examiner objected to the title and the abstract as not specific for the material being claimed at present. Applicant has amended the title and abstract, and respectfully requests withdrawal of the objection.

Rejections Under 35 U.S.C. § 112, First Paragraph

1. The Examiner rejected claims 36-38, 40, 42 and 51-54 under 35 U.S.C. § 112, first paragraph as allegedly lacking an adequate written description in the specification. Applicant respectfully requests reconsideration of the rejection.

Without conceding the correctness of the rejection, Applicant has amended the claims to recite that the methods use an antibody and/or an antigen binding portion thereof. Antibodies and antigen binding portions of antibodies are well known and have structures recognized in the art.

The Patent Office recognizes written description of antibodies when the antigen to which the antibodies bind is characterized. See MPEP 2163 II.A.3.: "disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public

depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen," citing Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004).

Here, the antigen is a known protein that is fully characterized by sequence and structure: von Willebrand factor (vWF).

Accordingly, Applicant is claiming antibodies and antigen binding portions thereof, which generally are well known in the art, and which bind to a fully characterized protein, vWF.

In addition, Applicant has provided in the specification, and has recited in the claims, an additional feature that provides more structure beyond that which is found acceptable (as noted above) by the USPTO for an adequate written description of antibodies: specific amino acid sequences. In contrast to disclosures of antibodies that provide *no* amino acid sequence, which the USPTO nevertheless has found to be adequately described (MPEP 2163 II.A.3.), Applicant has provided specific sequences of antibodies , which can only further convey to the skilled person that Applicant invented that which is now claimed.

Finally, Applicant has provided a number of embodiments in the specification that meet the elements of the claims. The following table describes the percent sequence identity to SEQ ID NO:3, SEQ ID NO:5 (the elected species), and SEQ ID NO:7, based on a BLAST comparison (using default parameters), with percent sequence identities more than 70% indicated in bold text:

SEQ	**% IDENTITY WITH:**		
ID NO	**SEQ ID NO:3**	**SEQ ID NO:5**	**SEQ ID NO:7**
1	**99**	68	66
2	**94**	69	66
3	**100**	69	66
4	64	**77**	65

5	69	**100**	**71**
6	65	**72**	**77**
7	66	**71**	**100**
8	66	**71**	**100**
9	**82**	**71**	**100**
10	**100**	**71**	**100**
11	**100**	69	66
12	**100**	**100**	**71**
13	**82**	**71**	**71**
14	**72**	**71**	**100**
15	**72**	**100**	**71**
20	66	**72**	**100**
21	**82**	**72**	65
22	69	**100**	**71**

Therefore, in addition to the other reasons mentioned above, the specification provides a representative number of species of the claimed genus.

Applicant therefore submits that the claimed invention is adequately described, and respectfully requests withdrawal of the rejection.

2. The Examiner rejected claims 36-38, 40, 42 and 51-54 under 35 U.S.C. § 112, first paragraph, as not enabled by the specification. Applicant respectfully requests reconsideration.

The Examiner appears to base the rejection on the teaching of Rudikoff et al., which the Examiner represents as teaching that "single amino acid changes in a CDR can abrogate the antigen binding function of an antibody." (Office Action at page 5). The Examiner analogizes that "mutating CDR residues in heavy chain antibodies is also unpredictable, especially given

that heavy chain antibodies comprise a smaller number of residues which contact antigen." (Office Action at page 6).

Applicant respectfully disagrees with the Examiner that the asserted unpredictability in making changes to CDRs of single domain antibodies, as claimed, would require undue experimentation such that the claimed invention would not be enabled. Applicant submits that there are several reasons why the changes to the claims as set forth by the Examiner would not require undue experimentation.

First, the specification provides extensive guidance for making and characterizing single domain antibodies that bind to vWF. For example, the working examples provide the following teachings that provide the person of ordinary skill in the art extensive guidance for producing the claimed products.

Examples 1-3 describe immunization of llamas, repertoire cloning, rescue of the library, and phage preparation.

Examples 4-16 provide guidance for producing vWF binding molecules that inhibit the interaction with collagen: selection for binders for vWF inhibiting the interaction with collagen first and second round of panning; functional characterization of vWF binders Inhibition of binding of vWF to collagen by VHH; expression and purification of VHH; ELISA binding to vWF; specificity of the VHHs; inhibition ELISA with purified VHH; sequencing of the clones; epitope mapping; expression and purification of bivalent and bispecific VHHs; binding in ELISA to vWF; inhibition ELISA with purified VHH; testing the stability of bivalent or bispecific constructs in human plasma; and evaluating inhibition by VHH at high shear.

Examples 17-25 provide guidance for selection of binders for vWF inhibiting the interaction with platelets: selection of binders for vWF inhibiting the interaction with platelets by panning; screening for binding to the A1 domain of vWF; selection of binders for vWF inhibiting the interaction with platelets MATCHM; ELISA binding to vWF of purified VHH;

inhibition ELISA with purified VHH; sequencing of the clones; evaluate inhibition by VHH at high shear; bivalent VHHs expression and purification; and evaluating inhibition by VHH at high shear.

Examples 26-30 provide guidance for making bispecific constructs for vWF-specific VHH: construction and sequence of bispecific constructs; expression and purification of bispecific constructs; binding to vWF; inhibition of binding of vWF to collagen by the bispecific constructs as compared to the monovalent VHHs; and evaluating inhibition by VHH at high shear.

Examples 63-64 provide guidance for humanization of vWF-specific VHH: alignment of C37 with DP-47; and mutagenesis of C37.

Examples 65-69 provide guidance for making fragments of anti-VWF VHHs: expression of a VHH-CDR3 fragment of vWF-C37; selection via first and second round biopanning on recombinant A1 (rA1); screening of individual clones after biopanning; determining restriction enzyme pattern and sequencing; and inhibition ELISA.

Thus, in addition to the high level of skill in the art generally, the specification provides far more than adequate guidance for practicing the claimed invention. Therefore, any experimentation is routine, not undue.

Second, the state of the art is far more advanced now, more than 25 years after the publication of the Rudikoff et al. article in 1982. Rudikoff et al. describe an investigation into "whether the limited number of amino acid substitutions presumably generated by somatic mutation can be effective in altering antigen binding specificity or affinity." (see page 1979, right column, second paragraph). Applicant notes, however, that the conclusion of Rudikoff et al. do not support unpredictability as suggested by the Examiner. Rudikoff et al. conclude that somatic mutation "may in *some* situations be effective in altering antigen-binding specificity." (emphasis in original; see Abstract). More to the point asserted by the Examiner, Rudikoff et al.

state that "it is clear that all such substitutions need not and probably do not affect antigen binding" (emphasis added) and further state that "as many as eight or nine substitutions may occur in hypervariable regions with no significant effect on hapten affinity or specificity." (emphasis added) (see page 1982, paragraph spanning left and right columns).

Moreover, even at that time of the publication of the Rudikoff et al. article, the person of ordinary skill in the art could readily have isolated variants with one or more amino acid changes in a CDR that nevertheless bind to antigen. This notion is in fact supported by the Rudikoff et al. article itself. At page 1982, right column, Rudikoff et al. state that where positive selection for antigen binding is used, the selection "will in general reveal only substitutions not producing large changes in antigen binding." Thus, the Rudikoff et al. article in fact supports Applicant's assertion that the skilled person would not require undue experimentation to make polypeptides of the claimed invention.

Third, the application provides a number of amino acid sequences of single domain antibodies that bind to vWF, which have at least 70% amino acid identity with e.g., SEQ ID NO:5 and which have vWF binding activity (see the table above). Therefore Applicant has provided a representative number of species of the examined species that demonstrate that sequence variation does not *per se* destroy the antigen-binding properties of the claimed single domain antibodies. This is consistent with the statements in Rudikoff et al. of using positive selection.

In addition, the application provides still more sequences that have less than 70% amino acid identity with e.g., SEQ ID NO:5 (that are not embraced by the examined species) yet which have vWF binding activity. Therefore, the Examiner's contention that the vWF binding activity is necessarily tied to amino acid sequence is not correct.

In view of the foregoing, Applicant submits that the claimed invention is fully enabled, and respectfully requests withdrawal of the rejection.

Rejections Under 35 U.S.C. § 102

The Examiner maintained the rejection of claims 1, 2, 22, 34-38, 40, 42-46, 51, 52, 54 and 55 under 35 U.S.C. § 102(e) as being anticipated by Frenken et al. (U.S. Patent No. 6,517,829). Applicant respectfully traverses the rejection and requests reconsideration.

The Examiner concedes that the Frenken et al. patent does not disclose antibodies that are specific for vWF. The Examiner asserts that certain claims, though not all of the rejected claims, claim a set of molecules having 70% or greater sequence identity variability such that one or more of the sequences provided in the Frenken et al. patent (in particular, the Examiner identifies SEQ ID NO:7 in the amino acid alignment with SEQ ID NO:5 of the instant application). Based on the sequence identity, the Examiner asserts that at the Frenken et al. patent anticipates the claimed invention.

The basis for this rejection is inherent anticipation based on the sequence(s) in the Frenken et al. patent. MPEP 2112 states that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art," citing Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). In this respect, the Examiner relies solely on sequence identity, but does not provide any evidence that the sequence of Frenken et al. binds to vWF. Thus, the Examiner has not provided the requisite evidence to show that the allegedly inherent characteristic (vWF binding) "necessarily flows from the teachings of the applied prior art".

Applicant notes that the CDRs of the Frenken et al. SEQ ID NO:7 and instant SEQ ID NO:5 are quite different in sequence, while the FRs of the sequences contain most of the identity. This is made clear when Frenken et al. SEQ ID NO:7is parsed into FRs and CDRs, as is shown below. The table shows the FR or CDR, corresponding amino acid sequence from SEQ ID

NO:7, and the number of amino acid differences between that amino acid sequence and the corresponding FR or CDR of SEQ ID NO:5 of the instant application:

Region	Amino Acid Sequence	Number of AA Differences
Framework 1	QVQLqESGGGLVQpGGSLRLSCAASGgTFS	3
CDR 1	wYAMG	1
Framework 2	WFRQAPGKEREFVA	0
CDR 2	tvSrgGGSTYYADSVKG	4
Framework 3	RFTISRDNAKNTVYLQMNSLKPEDTAaYYCaA	2
CDR 3	grgspsDTG-----RpdeYdY	15
Framework 4	WGQGTQVTVSS	0

The number of amino acid differences in the CDRs, in the aggregate, is 20, as compared to 5 amino acid differences in the framework regions in total (in a larger number of residues). Of particular importance, 15 of the amino acid changes in the CDRs occur in CDR3, which is traditionally implicated as the main component of binding by antibody molecules. Only 6 amino acids are the same in CDR3 of the Frenken et al. molecule as compared to SEQ ID NO:5, and these are scattered throughout the CDR3 sequence. Therefore, given the substantial divergence of the CDRs between these sequences, Applicant submits that Frenken et al. SEQ ID NO:7 is not likely to share the vWF binding property of instant SEQ ID NO:5.

Further, for inherent anticipation, an invention must be a necessary result of the prior art, not a probability or possibility. According to MPEP 2112, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" citing *inter alia* In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981)("To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "). *See also* Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991)("Inherency, however, may not be established by

probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." The theory of inherent anticipation serves to accommodate "situations where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges.")

Applicant's claimed invention is not a necessary result of the disclosure of the Frenken et al. patent. Frenken et al. does not disclose, expressly or inherently, all of the features of the claimed invention. Frenken et al. does not inherently provide the recited elements because each molecule disclosed by Frenken et al. does not have the properties required by the claimed invention.

Thus the molecules disclosed by Frenken et al. do not provide the recited elements of the claimed invention each and every time, and therefore Frenken et al. does not anticipate the claimed invention. Accordingly, withdrawal of the rejection of claims 1, 2, 22, 34-38, 40, 42-46, 51, 52, 54 and 55 under 35 U.S.C. § 102(e) is respectfully requested.

Rejections Under 35 U.S.C. § 103

1. The Examiner maintained the rejection of claims 1, 2, 22, 34, 35, 43, 44-50 and 55 under 35 U.S.C. § 103(a) as unpatentable over Nagano et al. (U.S. Patent No. 5,916,805) in view of Ghahroudi et al. (FEBS Lett. 1997, 414:521-526). Applicant respectfully requests reconsideration of the rejection.

The Examiner asserts that it would have been obvious to make a VHH that binds vWF based on the disclosure in Nagano et al. of antibodies that bind vWF and the disclosure in Ghahroudi et al. of method of obtaining VHH and the advantages of VHHs such as size, ease of purification and greater stability. In addition, the Examiner asserts that a skilled person would have been motivated to make the claimed invention based on the disclosure of utility of vWF

binding antibodies in Nagano et al. and based on the disclosure by Ghahroudi et al. of more stable, less expensive alternative antibody forms.

According to MPEP 2144.09, a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties, citing In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); and In re Wiechert, 370 F.2d 927, 152 USPQ 247 (CCPA 1967) (a 7-fold improvement of activity over the prior art held sufficient to rebut *prima facie* obviousness based on close structural similarity).

Applicant submits that the invention is not obvious based at least on unexpected results disclosed in the specification, consistent with MPEP 2144.09. Applicant described platelet aggregation and results obtained at high shear rates found *in vivo* beginning at page 16, line 11:

> Platelet aggregation is a very complex phenomenon and in an *in vivo* situation, the interaction of vWF with collagen only takes place at high shear as observed in small arteries. To assess platelet aggregation under high shear, the inventors performed perfusion experiments. Example 16 represents shear data obtained with the specific vWF-A3 binders SEQ ID No. 1 to 12. This experiment is representative for the interactions that take place upon damage of the vessel wall in a small artery (for example during angioplasty).

Example 16 on page 62 shows the evaluation of inhibition of platelet adhesion by VHH at high shear and low shear; results are summarized in Table 10 and 11. Table 10 shows inhibition of platelet aggregation at high shear (1600 s^{-1}), while Table 11 shows inhibition of platelet aggregation at low shear (300 s^{-1}).

Applicant discussed the unexpected nature of the results beginning at page 16, line 18:

> Surprisingly, monovalent VHH's perform very well in a platelet aggregation experiment under high shear: 50% inhibition of platelet aggregation was obtained at a concentration between 0.08 and 0.3 µg/ml. In comparison, the IgG vWF-specific antibody inhibiting the interaction with collagen, 82D6A3, inhibits 50% of platelet aggregation at approximately a twenty-fold higher concentration (Vanhoorelbeke K. *et al, Journal of Biological Chemistry*, 2003,

278: 37815-37821). These results were unexpected given that the IC50 values for the monovalent VHH's are up to 7 times fold worse in ELISA then the IC50 value of the IgG of 82D6A3.

These results show that monovalent vWF-binding VHHs were able to inhibit platelet aggregation to a greater extent than was expected based on the IC50 values of binding to vWF as assessed by ELISA. Specifically, platelet aggregation was inhibited using 20-fold less concentration of VHH than of monoclonal antibody 82D6A3. This was particularly surprising because the ID50 values of the VHH were 7 times worse than for the monoclonal antibody 82D6A3.

The IC50 of the monovalent vWF-binding VHHs in a platelet aggregation experiment under high shear also is surprising when compared to the humanized vWF monoclonal antibody AJW200. As described in Kageyama et al., *Arterioscler. Thromb. Vasc. Biol.* 2002 Jan.; 22:187-192 (of record), AJW200 has an IC50 under high shear induced platelet adhesion of about 2.6 μg/ml (see p. 189, right column), which is about a 10-fold higher concentration than the IC50 of monovalent vWF-binding VHH at high shear.

Thus, the data shows that an unexpectedly low concentration of monovalent vWF-binding VHH produces effective inhibition of platelet aggregation.

In addition, at page 17, line 12 of the specification, additional surprising features of the claimed molecules were set forth. Specifically, the smaller size of single domain antibodies is known and this gives rise to better penetration availability. However, it was unknown if VHHs could bind to vWF and inhibit the interactions of vWF effectively. Therefore, it was surprising to Applicant to find that indeed VHH were capable of this activity:

> Despite the small size of nanobodies, and thus advantages for penetration, it is still surprising that such a small molecule can inhibit interactions between large polymers such as vWF (up to 60 monomers) and collagen and with such a high efficiency. It has been described that only the large multimeric forms of vWF are hemostatically active (Furlan, M,. 1996, *Ann. Hematol.* 72:341-348).

> Binding of multimeric vWF to collagen occurs with ~100-fold higher affinity than binding of monomeric vWF fragments.

Further, it was unexpected that VHH would be sufficiently effective to be able to use a dose that would be consistent with therapeutic use. The specification describes this beginning at page 17, line 19.

> The results from the high shear experiments indicate that a lower dose may be administered to patients. Therefore, fewer side effects are expected (such as immunogenicity or bleeding problems).

Therefore, the application provides several examples of results that would not be expected by the person of ordinary skill in the art. Without knowledge of these unexpected results, the skilled person would not have a reasonable expectation of success in making the claimed invention, and indeed would not have been motivated to make a VHH that binds vWF due to the physical properties of vWF and the nature of platelet aggregation as discussed above. Therefore, Applicant submits that the claimed invention is not obvious over the combination of the Nagano et al. patent and the Ghahroudi et al. article.

Accordingly, Applicant respectfully requests withdrawal of the rejection.

2. The Examiner maintained the rejection of claims 56-59 under 35 U.S.C. § 103(a) as unpatentable over Nagano et al. (U.S. Patent No. 5,916,805) in view of Ghahroudi et al. (FEBS Lett. 1997, 414:521-526) and further in view of Griffiths et al. (U.S. Patent No. 5,670,132). Applicant respectfully requests reconsideration of the rejection.

Griffiths et al. discloses advantages of pegylating antibodies. Griffiths et al. does not, however, supply any of the elements missing from the combination of Nagano et al. and

Ghahroudi et al., and therefore the combination of Nagano et al., Ghahroudi et al. and Griffiths et al. does not render the claimed invention obvious.

Accordingly, Applicant respectfully requests withdrawal of the rejection.

Double Patenting Rejections

1. Claims 1, 2, 22, 34-38, 40 and 42-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-7, 16, 18, 19, 45, 56 and 66 of copending Application No. 10/534,349. Applicant respectfully requests reconsideration. Because the instant claims are not at present allowable, Applicant defers addressing this rejection until a later date.

2. Claims 56-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-7, 16, 18, 19, 45, 56 and 66 of copending Application No. 10/534,349 in view of Griffiths et al. (U.S. Patent No. 5,670,132).. Applicant respectfully requests reconsideration. Because the instant claims are not at present allowable, Applicant defers addressing this rejection until a later date.

CONCLUSION

In view of the foregoing, the present application is believed to be in condition for allowance. A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the application in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, any necessary extension of time is hereby requested. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. A0848.70010US00.

Respectfully submitted,

Dated: May 11, 2009

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